Modified PTO/SB/33 (10-05)

| PRE-APPEAL BRIEF REQUEST FOR REVIEW | Docket Number<br>Q80490 | |
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| | Application Number<br>10/805,220 | Filed<br>March 22, 2004 |
| Mail Stop AF<br>Commissioner for Patents<br>P.O. Box 1450 Alexandria, VA 22313-1450 | First Named Inventor<br>Kazunari YAMAGUCHI et al | |
| | Art Unit<br>1648 | Examiner<br>Chen, Stacy |

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Applicants request review of the final obviousness rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the attached sheet.
Note: No more than five (5) pages may be provided.

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**Reason forWhich Review is Requested**

To maintain a rejection under 35 U.S.C. §103 the cited references must teach or suggest each and every element of the claim. It is necessary to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some *articulated reasoning* with some *rational underpinning* to support the legal conclusion of obviousness. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.[1] The Guidelines indicate a rationale *must* be set forth as to why the claimed invention is obvious and refer to rationales predicated on predictability.[2] Thus, according to the Guidelines, predictability is a key determinant in an obviousness analysis, particularly in an unpredictable art such as biotechnology. A *prima facie* case of obviousness may be rebutted by a showing of unexpectedly superior properties of the claimed invention compared to the closest prior art which is commensurate with the claims. Use of hindsight is improper in determining whether a combination is obvious therefore, obviousness is found only where the prior art contains a teaching, suggestion or motivation to combine the individual elements.

The Office failed to establish a *prima facie* case of obviousness. The Office failed to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does; the Office asserts mere conclusory statements (i.e., that one of skill would be motivated to include p10 and expect enhanced sensitivity), unsupported and contradictory to the cited references; the Office failed to set forth an

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[1] *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), wherein the Court reiterated, an analysis for determining obviousness must include analysis of the underlying factual inquiries including, (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art.

[2] Federal Register, Vol. 72, No. 195, Wednesday, October 10, 2007. For example, combining prior art elements according to known methods to yield *predictable* results, simple substitution of one known element for another to obtain *predictable* results, use of a known technique to improve similar devices in the *same* way; applying a known technique to a known device ready for improvement to yield *predictable* results; choosing from a finite number of identified, *predictable* solutions, known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been *predictable* to one of ordinary skill in the art and some teaching, suggestion, or motivation in the prior art that *would have led* one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

articulated reasoning with a rational underpinning to support the rejection; the Office failed to appreciate the unpredictability in the art; the Office failed to properly analyze the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art; the Office failed to follow Office Guidelines; the Office failed to appreciate Applicants' unexpectedly superior results; and the Office used impermissible hindsight in making the rejection.

Carbone does not disclose use of IgM antibodies in determining infection by BDV. One of ordinary skill in the art would reasonably expect that IgM antibodies to BDV, if detectable, quickly disappear, approximately one month after their appearance, and are replaced by IgG antibodies. Specification, page 2, the 1st full paragraph. Thus, one of ordinary skill in the art would understand that Carbone suggests, if anything, a method of detecting IgG alone, particularly since it is not always possible to obtain acute phase serum in natural BDV infections. Carbone, page 516, column 1, line 37-40. The Office is incorrect in ignoring and according no weight to Applicants' teachings of the benefits of assaying both IgM and IgG because this teaching makes it unlikely that before Applicants' teachings one of ordinary skill in the art would have had a reasonable expectation that testing both IgM and IgG antibodies would increase the sensitivity in detecting an infection.

Carbone discloses unpredictability in BDV detection. Diagnostic tests are discussed in Carbone in detail, *inter alia*, at pages 515 to 520. Carbone indicates, "BDV infection is complex and the infectious stage is unpredictable to know." Page 516, column 2. Regarding Immunoflourescence Assays, Carbone indicates, "the major technical concerns with the IFA technique are specificity and the variability introduced by reader expertise (i.e., correct recognition of the specific, characteristic pattern of BDV antigens in the infected cell" and "...reader to reader variability in testing makes it difficult or impossible to replicate serology results among independent laboratories." Page 518, column 1. Regarding Immunoblot Assays, Carbone states, "although not proven for BDV proteins, both nonhuman glycosylation patterns of virus antigens as well as the typical protein-reducing and -denaturing characteristics of the gel can destroy or alter conformational virus epitopes." Page 518, column 2, ¶ 3. Carbone continues, "drawbacks of the IB technique include the time-consuming and costly nature of this technique and the disadvantage that the high specificity screen with IB may be accompanied by some decrease in sensitivity of the test."

Page 518, column 2, first ¶. Regarding ELISA, Carbone states, "BDV-specific ELISAs have been reported to have some difficulty with sensitivity" and "it is unclear whether the inability of these ELISAs to detect anti-BDV antibody in humans, where anti-BDV antibody titers are generally low, represents a false-negative due to species specific variability in the sensitivity of the ELISA or a true-negative result…", "specificity concerns with these ELISAs are demonstrated when human sera shown seronegative by IB give a positive result in ELISA due to non-specific reactivity." Page 518, column 2, second full ¶. As to molecular diagnostic methods, Carbone states, "the presence of RT-PCR inhibitors, such as heparin or hemoglobin in an blood sample, may result in false-negative results." Page 520, third full ¶. Carbone also indicates, "a low level of viral RNA in peripheral blood may fall below the detection sensitivity of RT-PCR and produce false negative results." The reference states, the "ability of BDV primers designed from animal virus sequences to recognize a putative human BDV also needs to be taken into account" and is therefore yet another factor contributing to the unpredictability of diagnosis. Page 520, first column, last ¶.

Regarding confirmation of a potentially positive test result, Carbone states, "using the sequence to confirm the source of the recovered strain, e.g., to distinguish a human BDV strain from a laboratory contaminant, is not feasible at present." Page 520, second column, third full ¶. Confirmation is also unpredictable due to BDV being a "cell-associated virus, and it is difficult to recover infectious virus from bodily fluids." Page 520, column 2, fourth ¶. Further, infectious virus isolation testing is unpredictable because of "…the low level of infectious BDV replication in some species (probably including humans)." Pages 520-521, last ¶. Carbone states, as a Conclusion of the research, "what *is needed first* is a validated assay or series of assays that are capable of reliably identifying BDV infection in humans." [Emphasis added.] Page 523, second column, fourth full ¶.

Thus, the reference supports Applicants' position that due at least to the unpredictable nature of BDV diagnosis, a facet of BDV diagnosis ignored by the Office in making the outstanding rejection but required to be considered in making an obviousness determination, Applicants' claimed invention is non-obvious and the rejection should be withdrawn.

Yamaguchi et al. underscore the unpredictability in diagnosis of BDV infection and teach away from the combination of antibodies recited in Applicants' claims. For example, Yamaguchi et al. state, "IFA does not always give definite results, due to the existence of cell specific auto-

antibodies, the variability of subjective interpretation, and insufficient sensitivity in detecting low titer antibodies." Page 349, column 1. The reference states, "although IP and WB analyses may be more reliable and specific than IFA, these methods are time consuming and expensive and therefore unsuitable for large-scale screening." Page 349, column 1. Yamaguchi et al. teach away from the combination suggested by the Office, because the reference definitively states, "the p40 and p20, expressed at high levels in the rat brain and infected cells, represent good markers with which to search for evidence of BDV infection in animal and human cells." Page 354, column 1. Therefore, according to Yamaguchi et al. in 2001, one of ordinary skill in the art would have reasonably expected that p40 and p20 assays alone were sufficient diagnostic assays making an appreciation of adding p10 highly unreasonable and contrary to common sense. The teaching away in Yamaguchi et al. contrasts Applicants' comparative data, which teaches, in Comparative Example 1, dramatic improvement of BDV detection when p10 antibodies are included in the assay. Specification, pages 22-25, Table 1. Table 1 teaches that 17 out of 23 specimens (73.9%) were positive for BDV infection when p24 and p40 antibodies were used in the assay but that by including p10 antibodies the results increase to 95.7%. 5 out of 23 specimens were detected with p10 antibodies but not with p24 nor with p40 antibodies.

Regarding Watanabe et al., the reference states, "the results in this study *could be worthy* for establishment of diagnostics method for BDV infection." [Emphasis added.] Page 777, column 2. The Office misconstrues the reference, stating, "antibodies to individual viral proteins and BDV specific antigens are useful for establishing diagnostic methods", which is inaccurate and misinterprets the reference.

The Office ignored significant passages of Planz et al. which underscore the unpredictability in BDV diagnosis relevant to the patentability of Applicants' claimed invention. The Office ignored the statement, "due to conflicting results obtained in attempts to detect viral nucleic acid consistently in human blood from psychiatric patients, this issue is still controversial." Page 6251, column 1. Planz et al. disclose, "sera were obtained from all three patients and tested either in Western blot analysis or by immunofluorescence for the presence of BDV specific antibodies" and "interestingly, in these sera, no virus specific antibodies could be detected, even at dilutions of 1:2 in immunofluorescence." Page 6255, first column, first ¶. The title of the paper alone rebuts the Office's position indicating infection of the granulocyte fraction absent antiviral

antibodies. The observations in Planz et al. rebut the Examiner's conclusion of obviousness because Planz et al. teach away from the use of sera based detection methods of BDV.

Regarding Hatalski et al., the reference reveals the unpredictability in the field of BDV diagnosis and teaches away from Applicants' claimed combination method. For example, Hatalski et al. fail to identify p10 as being important in BDV infection detection. Page 741, first column. Hatalski et al. focus the attention of one having ordinary skill in the art to gp18, not p10. Page 741, first column. Hatalski et al. state, "the presence or absence of neutralizing antibodies in BDV-infected animals has been controversial…some reports have not shown evidence for neutralizing antibodies; however, this may reflect different time points for collection of sera or variation in the assay system for neutralization." Page 744-745, second column, Discussion. Hatalski et al. indicates, "there are several plausible explanations for the late appearance of neutralizing antibodies in Borna disease. One possibility is that, in the early disease, gp18 is expressed at lower levels than the 40- and 23-kDa viral proteins, which elicit high titer antibodies" and " the role of neutralizing antibodies in Borna disease is less clear, given [that] the central nervous system viral titers remain elevated in the presence of neutralizing antibodies in serum and cerebrospinal fluid." Page 745, second column, last ¶.

For at least the aforementioned reasons, the Office failed to establish a *prima facie* case of obviousness, failed to consider Applicants' unexpected superior properties, failed to follow Office Guidelines and used impermissible hindsight in making the rejection. The rejection should therefore be withdrawn.